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THERAPEUTIC AGENT FOR THE ORAL REGION

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THERAPEUTIC AGENT FOR THE ORAL REGION

[Therapeutikum für den Mundbereich]

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The invention concerns a therapeutic agent for the oral region and its use, especially for prevention and treatment of periodontal diseases.

There is a broad spectrum of applications in medicine for ethylenediaminetetraacetic acid (EDTA), especially in the form of its disodium salt (NaEDTA). In clinical practice it is used successfully, for example, in the treatment of heavy metal poisonings, to resolve kidney stones, to lower the calcium level in the blood and to improve circulation in arteries in the elderly.

Moreover, it is known that the cell surface of mainly gram-negative, but also certain gram-positive bacteria is damaged by exposure to EDTA. Tris buffers enhance the effects of EDTA. Gram-negative bacteria that are exposed to EDTA show increasing permeability (i.e., increased cell wall permeability with corresponding disruption of the internal equilibrium) to extracellular solutions and leakage of intracellular solutions. Moreover, they are sensitized to lysozyme, an endogenous defense system, bactericides and antibiotics, and they release from the cell wall periplasmic enzymes and proteins associated with the cell membrane as well as lipopolysaccharides, proteins, phospholipids and divalent cations. Thus, the use of EDTA-tris leads to a potentiation of the effect of antimicrobial agents. Hitherto EDTA was used as an antimicrobial substance only in some areas of veterinary medicine.

There is no doubt that microorganisms play the key role in the development of inflammatory gingival and periodontal diseases. A number of studies in recent years have proven that the relative buildup of various specific microorganisms, above all gram-negative anaerobic bacteria is typical for certain disease patterns of the periodontium. In contrast, mostly gram-positive microbes, specifically up to 85%, are found in the chiefly supragingival plaque of the clinically healthy periodontium.

In gingivitis the amount of bacilli and the amount of gram-negative bacteria increase (55% gram-positive bacteria; 45% gram-negative bacteria, of which 50% are obligate anaerobes).

In true periodontitis there is a further increase of gram-negative anaerobic microbes. In an aseptic test animal all of the pathogens that are found in this case produce pathological changes at the periodontium, which are for the most part expressed in massive bone loss. Up to now attempts were made to eliminate bacterial plaque by using numerous chemotherapeutic agents. The effect of these substances varies.

For example, bactericides that inhibit the multiplication of the bacteria were used. In addition, the number of microorganisms was reduced through the use of metal salts or enzyme derivatives. Moreover, the enzymic activity of the bacteria, primarily acid formation, was disrupted or suppressed through suitable agents. However, none of these agents was able to prevent periodontal diseases effectively.

One agent that has been widely used in the last 15 years to treat periodontal diseases is chlorohexidine digluconate, which inhibits plaque formation, and can reduce gingivitis or keep it from developing and can bring about an up to 73% reduction of the formation of tartar. However, it has a bacteriostatic effect only against gram-positive pathogens, but this agent does not combat the main sources of periodontal diseases, namely gram-negative pathogens. A decrease of the sensitivity of oral microorganisms to chlorohexidine preparations will further limit the use of this agent in the future. In addition, a disadvantage with chlorohexidine-containing agents is the bitter taste and the loss of taste sensation after using them for 2-3 weeks, although this is reversible.

Therefore, the task of this invention is to make available a therapeutic agent for topical oral application that has a pleasant taste, is free of side effects, and guarantees effective control especially of gram-negative bacteria. In particular, the task lies in specifying an effective chemotherapeutic agent for combating periodontal disease.

The invention solves this task by a therapeutic agent for the oral region that contains EDTA. This therapeutic agent is free of side effects in topical oral application and is practically not absorbed in the intestine. EDTA, which is a standard medicine used as an antidote for heavy metal poisonings and in the treatment of arteriosclerosis in humans, is being used for the first time as an antibacterial agent in human medicine.

It proved to be favorable for the EDTA to be in the form of an alkali salt, preferably as NaEDTA. Solid, paste or liquid substances are possibilities as carrier materials for the EDTA. Paste or liquid carriers are especially suitable. A liquid carrier preferably consists of distilled or demineralized water or an aqueous solution.

Although there are no specific limits for the content of EDTA in the therapeutic agent, it is advantageous to use it in amounts of 0.2-1.0 wt%, preferably 0.4-0.8 wt%, especially preferably about 0.6 wt%.

Therapeutically positive effects can also be seen if, for example, pure NaEDTA is administered in an aqueous solution. Such a solution has a pH of 3.93. However, it is better to establish the pH of the solution to a value between 5 and 9, with a pH of about 8 being preferably chosen. The pH can be adjusted by means of suitable basic substances, for example, a dilute NaOH solution.

It is especially advantageous to add tris(hydroxylmethyl)aminomethane to the therapeutic agent, thus producing EDTA-tris. This compound additionally brings about a significant enhancement of the antiphlogistic effect of the therapeutic agent. Since a tris(hydroxymethyl)aminomethane solution has a basic reaction, it can optionally also be used to establish a desired pH value. The therapeutic agent in accordance with the invention can contain still other conventional additives, in addition to EDTA and, optionally, tris(hydroxymethyl)aminomethane. Examples here are astringents such as alpha-bisabolol, and

hamamelis extract, flavorings as well as emulsifiers, which can be used individually or in combination.

Unexpected synergistic effects are achieved in combating periodontal diseases when EDTA-tris and astringents are administered in a combination, so that an especially preferred embodiment of the therapeutic agent in accordance with the invention contains at least these two components. The basis for this favorable interaction is still not known, but it was unequivocally shown that the antibacterial effect of EDTA-tris is significantly improved through the addition of astringents.

Finally, the therapeutic agent in accordance with the invention can also additionally contain vitamin A and/or vitamin E. These vitamins serve firstly as antioxidants, which counteract a pathologically elevated formation of the so-called "free oxygen radicals" (FR).

These FRs have an unshared electron in the outer shell, due to which they are extremely unstable and react practically spontaneously with any compound in their environment. Many chemical reactions with FRs occur in the body under normal conditions and are necessary to maintain health. Due to the effect of pathological factors on the process of the origination of FRs their amount increases, due to which in turn they can then give rise to numerous pathological phenomena.

The extent to which pathologically elevated FR concentrations play a role in periodontal diseases is still not precisely known. However, it has been shown that FRs have a central function in the nonspecific cellular immune defense by macrophages. In the course of the defense reaction of the macrophages to an exogenous antigen a sharp increase of the activity of FRs was measured in the macrophages, and the antigen is practically "incinerated" by the macrophages. If there are disruptions in the formation of FRs in the macrophages and if there is chronic overload of macrophages by too many antigens and antigens appear for too long a time, incineration of the macrophages themselves can take place, with subsequent breakdown of the local immune response and uncontrolled spread of the antigens (for example, bacteria).

Thus, it is clear that bacterially caused periodontal disease can in a certain way be due to an insufficient immune defense. Therefore, in such cases it is a good idea to add vitamin A and/or vitamin E to the therapeutic agent in accordance with the invention to support the natural immune defense.

The EDTA-containing therapeutic agent in accordance with the invention can be used advantageously as an agent for care of the oral and throat region.

In addition, the therapeutic agent in accordance with the invention can be used especially advantageously for prevention and treatment of periodontal diseases, as will be made clear from the following example.

Example

A ready-to-use mouth rinse of the following composition was prepared (data in wt%):

NaEDTA	0.60
alpha-Bisabolol	0.005
Hamamelis extract	0.10
Flavoring	0.12
Distilled water	98.54
Emulsifier 1	0.625
Emulsifier 2	0.01

In addition, tris(hydroxymethyl)aminomethane is added to this aqueous solution until the solution has a pH of 8.

The above-described therapeutic agent in accordance with the invention in the form of an oral rinse solution was used to test its curative effect on inflammatory processes of periodontal tissue. The tested patients suffered from chronic catarrhal gingivitis and periodontitis. The originally treated group consisted of 18 patients. After normal dental care with a toothbrush and commercial toothpaste the patients rinsed their mouth with the oral rinse solution in accordance with the invention twice daily for a period of 10 min. The patients found the taste of the oral rinse solution to be pleasant. Side effects caused by the therapeutic agent in accordance with the invention were not observed during the test period and also beyond it.

The degree of the periodontal disease was established before treatment and the results of the treatment with the oral rinse solution in accordance with the invention were then determined clinically and histologically.

The clinical test was done by determining the gingiva index (GI) according to Silnes-Löe (1967), in which the inflammatory changes of the gingiva were macroscopically investigated and classified as follows on a scale of 0-3:

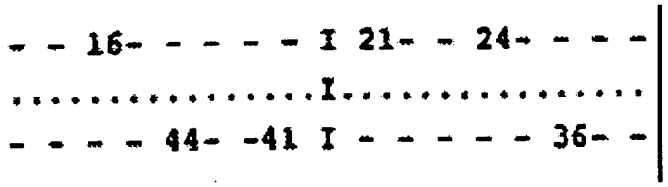
0—Gingiva without signs of inflammatory change,

1—mild inflammation, slight change in color and structure,

2—moderate inflammation, moderate reddening with edema and hypertrophy, bleeding when pressed,

3—severe inflammatory changes, significant reddening, hypertrophy, spontaneous bleeding, ulcering.

The gingiva index of an individual is determined by the average value of the GI of all of the tested individual teeth. The series of the tested teeth includes:



The gingiva index of all teeth was determined before treatment for all of the patients and also 2 and 3 weeks after the beginning of treatment.

For the histological (microscope) investigation of the inflamed gingival changes parts of the interdental gingiva both in the front and premolar region in the lower and upper jaw were removed and collected before the beginning of treatment and 2 and 3 weeks after the beginning of treatment. The combined tissue samples were fixed in 10% formaldehyde, processed by conventional histological techniques, and stained with hematoxilin-eosin.

The histological picture was characterized as follows with regard to the success of treatment of the inflammatory gingival changes with respect to persistent chronic inflamed infiltrates of the connective tissue and regression of epithelial proliferations:

a) in the case of patients with very good results in comparison to the initial state, i.e., before treatment, only a slight thickening of the superficial functional epithelium was observed, under which a slight (vanishingly small) round cell infiltrate remained. The infiltrate surrounding the vessels of the corium disappeared.

b) In the group with good treatment result the thickening of the superficial epithelium and vessels enlarged in the corium with loosening of the connective tissue still exist. The round cell infiltrates were greatly reduced in size or had disappeared completely.

c) In the cases with satisfactory result slight thickening of the superficial epithelium with keratinization in places was seen. Numerous vessels with large round cell infiltrates were still found in the deep layers.

d) In the case of an unsatisfactory result the original histological picture of the tested intradental papillae was unchanged after 2 or 3 weeks.

The evaluation of the clinical and histological tests gave the following result:

Of 18 patients in the original group 16 were investigated clinically and 15 histologically after 2 weeks, since in one preparation (sample) no corium was removed along with other tissue and thus the examination of the inflammatory changes was not possible. After 3 weeks of treatment it was only possible to investigate 8 patients clinically and histologically. The other 8 did not appear for the examination considering that their complaints had disappeared and the wish to avoid the removal of interdental papillae.

After two weeks of treatment both subjective and objective improvement of the inflammatory, clinically observable changes was confirmed in all 16 tested patients. 3 weeks

after the beginning of treatment a further clinical improvement was seen in 6 of the 8 patients that appeared for the last examination, compared to the condition after 2 weeks of treatment, while in 2 patients no change of the GI was found when compared to the condition after 2 weeks of treatment. However, when compared with the original condition before the beginning of treatment all of the patients showed an improvement. The GI values of the patients after 2 weeks of treatment had decreased by an average of 1.15, from an original average GI value of 1.56 to 0.41. The least difference in the GI values, i.e., the smallest therapeutic effect, was observed in the frontal segment of the lower jaw, where the average GI value had decreased from 1.60 before treatment to 0.73 after 2 weeks of treatment.

Out of 15 histologically examined patients 11 showed an improvement of the inflamed conditions after 2 weeks of treatment. Of these 5 had very good results, 5 had good results, and a satisfactory result was achieved in one case. Only in 4 cases were no changes seen in the histological findings. These cases must be classified as unsatisfactory. Very probably this was caused by a greater extent of the inflammation, in the sense of periodontitis with deep periodontal pockets, the presence of subgingival tartar and a considerable amount of microbial plaque. After 3 weeks of treatment a histological improvement was observed in all of 8 of the patients who were still available.

The probability of the reliability of the improvement of the histological picture after treatment with the therapeutic agent in accordance with the invention was determined by a so-called parametric sign test. The improvement (+) appeared 11 times, no improvement (-) appeared 4 times. The critical value for $n = 15$ is 4 for a 90% probability.

Comparison of the clinical examination results (according to the GI) with the histological results showed that correspondence in the improvement occurred in those cases in which the average GI value before treatment was no higher than 1.83. The cases in which the GI value was higher than 1.83 remained histologically unchanged.

Thus, the clinical study of the therapeutic effect by means of the gingiva index of a patient showed a 100% therapeutic effect, while the histological study showed a 90% effect. The histological picture of the inflamed papillae remained unchanged only in four patients, even though the subjective and clinical signs (according to the GI) showed an improvement for these patients.

One of the main reasons for the less than 100% therapeutic effect of the therapeutic agent in accordance with the invention with regard to the histological finding could lie in the poor discipline of the tested patients, who did not precisely follow the instructions of the physician.

A bactericidal and bacteriostatic effect of the EDTA-containing therapeutic agent in accordance with the invention for topical oral use was shown by a reduction, in some patients even a complete disappearance, of the round cell infiltrates in the gingival region. A positive

curative effect of the therapeutic agent in accordance with the invention was seen in patients who suffered from catarrhal gingivitis and periodontitis. The therapeutic agent in accordance with the invention thus is a pleasant tasting, side effect free, effective agent for combating periodontal diseases.

To demonstrate that the therapeutic agent in accordance with the invention attacks the dental plaque, first, i.e., first of all, the bacteria, but not the hard substances of the teeth like the enamel/dentin and root element, the following test was also carried out. 100 extracted teeth were kept for 3 weeks in the ready-to-use oral rinse solution mentioned above. The solution was then tested for an increase of the calcium phosphate content (the hard substances of the teeth consist of up to 96% of this substance). This test showed that no calcium phosphate was dissolved out of the crystals of the hard substances of the teeth by the EDTA of the therapeutic agent in accordance with the invention. The active agent concentration is probably too low for this and the binding of the calcium phosphates in the prisms of the dental hard substances is too strong.

Claims

1. A therapeutic agent for the oral region characterized by a content of EDTA.

2. A therapeutic agent as in Claim 1, which is characterized by the fact that the EDTA is in the form of an alkali salt, preferably the sodium salt.

3. A therapeutic agent as in Claim 1 or 2, which is characterized by the fact that the EDTA is contained in a carrier, preferably a paste or liquid carrier.

4. A therapeutic agent as in Claim 3, which is characterized by the fact that distilled water or an aqueous solution serves as carrier.

5. A therapeutic agent as in one of the preceding claims, which is characterized by the fact that the content of EDTA is 0.2-1.0 wt%, preferably 0.4-0.8 wt%, especially preferably about 0.6 wt%.

6. A therapeutic agent as in one of the preceding claims, which is characterized by a pH value of 5-9, preferably about 8.

7. A therapeutic agent as in one of the preceding claims, which is characterized by a content of tris(hydroxymethyl)aminomethane.

8. A therapeutic agent as in one of the preceding claims, which is characterized by a content of vitamin A and/or vitamin E.

9. A therapeutic agent as in one of the preceding claims, which is characterized by an addition of one or more astringents, one or more flavoring agents, and/or one or more emulsifiers.

10. A therapeutic agent as in Claim 9, which is characterized by a content of 0.6 wt% NaEDTA, 0.005 wt% alpha-bisabolol, 0.10 wt% hamamelis extract, 0.12 wt% flavoring agent,

0.625 wt% of a first emulsifier, 0.01 wt% of a second emulsifier, and distilled or demineralized water as the remainder.

11. A therapeutic agent as in Claim 10, which is characterized by the fact that the pH is adjusted to 8 by means of tris(hydroxymethyl)aminomethane.

12. The use of EDTA to produce a therapeutic agent as in one of Claims 1-11 for prevention and treatment of periodontal diseases.

13. The use of an EDTA-containing agent, especially as in one of Claims 1-11, for care of the mouth and throat, especially for prevention and treatment of periodontal diseases.